ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ijpgderma.org

Indian Journal of Postgraduate Dermatology

Review Article

Imiquimod: Newer Perspectives to an Old Drug

Sonali Gupta[1], Pooja Agarwal[1], Kalgi Baxi[1], Abhishek Nyati[2]

[1]Department of Dermatology, Smt. Nathiba Hargovandas Lakhmichand (NHL) Medical College, [2]Department of Oncology, Byramjee Jeejeebhoy Medical College (BJMC), Ahmedabad, Gujarat, India.

***Corresponding author:**
Sonali Gupta,
Department of Dermatology, Smt. Nathiba Hargovandas Lakhmichand (NHL) Medical College, Ahmedabad, Gujarat, India.

dr.sonali42@gmail.com

Received: 18 October 2023
Accepted: 19 December 2023
Published: 12 February 2024

DOI
10.25259/IJPGD_99_2023

Quick Response Code:

ABSTRACT

Imiquimod is a topical age-old drug belonging to the imidazoquinolones class which acts by modulating the immune system. It has been approved by the US Food and Drug Administration for treating external genital and perianal warts, actinic keratoses and superficial basal cell carcinoma. Along with these, there have been a large number of diseases for which the drug has played a beneficial role with a good safety profile.

Keywords: Actinic keratosis, Anogenital warts, Imiquimod, Superficial basal cell carcinoma

INTRODUCTION

Imiquimod is a synthetic compound that belongs to the imidazoquinolones class of drugs. It acts as an immune response modifier in the body and also has potent anti-viral and anti-tumour activity. It's role as an immune response modifier was discovered while screening various drugs for anti-herpetic activity.[1]

PHARMACOKINETICS

Topical imiquimod has minimal systemic absorption. Less than 0.9% of the dose is excreted in the urine and faeces.[1] The systemic exposure of drug is more dependent on the surface area of application than the amount of applied dose. The apparent half-life of the 5% cream applied topically is about 10 times greater as compared to the half life seen after following subcutaneous injection, which suggests its prolonged retention after topical application.

CONCENTRATIONS AVAILABLE AND ADMINISTRATION

Imiquimod is available in 2.5%, 3.75% and 5% concentration.

A thin layer of cream is to be applied and left overnight for 6–10 hours (Centres for Disease Control and Prevention guidelines), after which the area is washed with mild soap and water to remove any cream.

a. Anogenital warts – Application is for 3 days a week overnight up to a maximum of 16 weeks
b. Basal cell carcinoma (BCC) – Once a day for 5 days a week on the lesion and the immediate surrounding area for 6 weeks.
c. Actinic keratosis (AK) – Should be applied for 2 days a week for 16 weeks. It should not be applied to an area larger than patient's forehead or cheek (about 2 inches by 2 inches).

MECHANISM OF ACTION

Two mechanisms have been attributed to the efficacy of imiquimod in dermatology. They include immunomodulatory and anti-tumour (direct/indirect) actions.

Immunomodulatory action

Imiquimod acts as an agonist on toll-like receptors 7 and 8, which through a cascade of events leads to the induction of proinflammatory cytokines and chemokines along with activation of antigen presenting cells and innate immunity [Figure 1] causes activation of nuclear factor-kappa B which leads to the induction of proinflammatory cytokines and chemokines such as interferon-gamma (IFN-g), interferon-alpha and interleukin-12 (IL-12). This further leads to the activation of antigen-presenting cells and other components of innate immunity and, eventually, a profound T-helper (Th1) cellular immune response gets initiated. The mounting of T-helper Type 2 (Th-2) immune response is simultaneously inhibited.

It also induces the migration of Langerhans cells to regional lymph nodes and enhances the antigen presentation to naive T-cells and thus perpetuating the cycle of T-cell response.

Anti-tumour action

Direct action

This is the main anti-tumour mechanism of imiquimod. Apoptosis in tumour cell lines is induced by activation of the workhorses of apoptosis (the caspase family of proteases) by intrinsic pathway.[2] It can also independently upregulate proapoptotic proteins of the Bcl-2 family of proteins [Figure 2].

Indirect actions

Indirect actions of imiquimod occur by inducing the release of various cytokines which, then, stimulate a cell-mediated immune response and contribute in drug's anti-tumour activity.[3] The main cytokines induced include IL-12, tumour necrosis factor-alpha and IFN-g. These cytokines block angiogenesis and increase the levels of cytotoxic T-cells and natural killer cells in the local milieu by induction of 2'-5'-oligoadenylate synthetase.[4] Further, there has been an increase in IL-12 which down-regulates IL-10 and thus stimulates anti-tumour T-cells which are responsible for killing malignant cells.

INDICATIONS

Details of each have been described below [Table 1].

Anogenital warts

The first clinical application in which imiquimod proved useful was for genital warts. The common therapeutic problems with anogenital warts are recurrence and long duration. The reason for this could be that most treatment therapies target physical destruction of the disease rather than direct antiviral activity against the human papillomavirus. Imiquimod represents a significant advancement in the treatment due to its antiviral

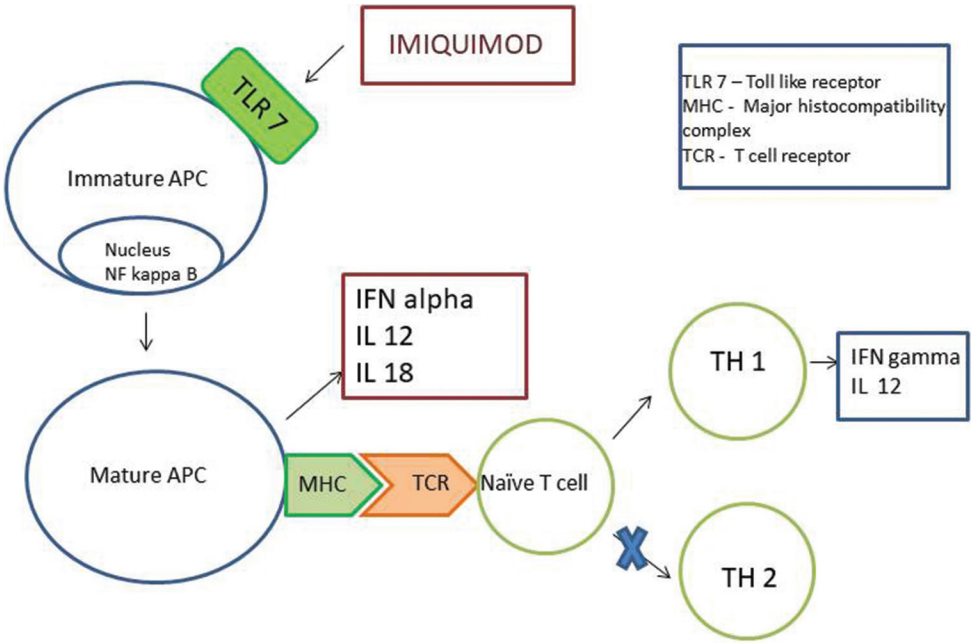

Figure 1: Immunomodulatory mechanism of imiquimod.

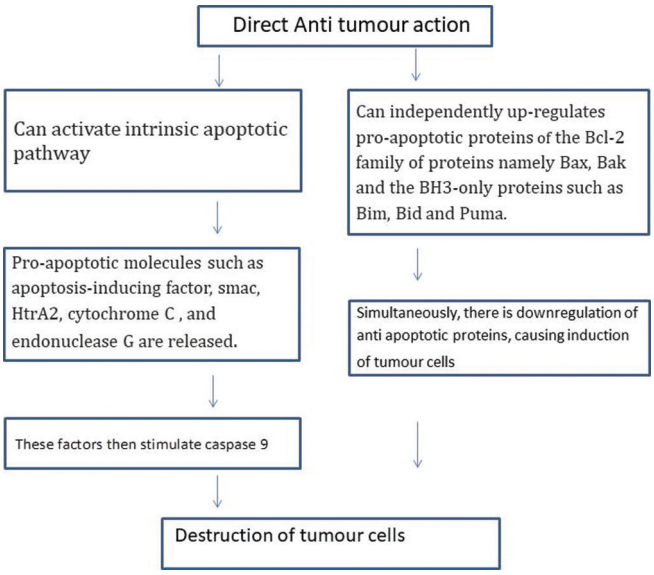

Figure 2: Direct anti-tumour action mechanism of imiquimod.

and non-destructive properties. It has been Food and Drug Administration (FDA) approved in 5% cream formulation for overnight application (6–10 h) over warts 3 times a week for up to 16 weeks and 3.75% daily for up to 8 weeks (~50% clearance and ~30% clearance, respectively).[5] Although there have been various modalities of treatment such as excision, electrocautery and laser vaporisation which can be used to remove warts quickly, there have been many disadvantages as they are painful, destructive and recurrences are common with these modalities (i.e., occurring in 9–72% of warts treated with ablative laser therapy).[6] Imiquimod 5% cream showed some clearance of warts in immunosuppressed human immunodeficiency virus-infected patients with genital warts also. Major advantage of imiquimod lies in its self-application at home which decreases the hospital visits and increases compliance of the patient toward treatment. By virtue of increase in cellular immunity, it gives long-term protection against recurrences or reinfection[1] and, hence, serves as a better alternative for genital warts [Table 2].[7-15]

Actinic keratoses

Imiquimod 5% cream was first approved by the FDA in 2004 and all the three concentrations have been approved. Application of 3.75% cream daily for 2 weeks have shown similar efficacy with fewer cutaneous adverse effects as 5% cream twice weekly for up to 16 weeks (~50% and ~35% clearance, respectively). Another added advantage witnessed with the lower concentration of imiquimod was the wider surface area of application (i.e., 200 cm^2 as compared to 25 cm^2 for the 5% preparation of imiquimod).[16]

Imiquimod produces its activity through augmented antigen recognition and amplified cellular immunologic response

Table 1: Indications of Imiquimod.

FDA approved	Off label dermatological indications
Anogenital warts	Common warts
Actinic keratoses	Molluscum contagiosum
Superficial basal cell carcinoma	Keloids
	Nodular and morphoeic basal cell carcinoma
	Squamous cell carcinoma in situ
	Invasive squamous cell carcinoma
	Melanoma
	Mycosis fungoides
	Infantile haemangioma

FDA: Food and drug administration

which causes development of immunologic memory and serves to reduce the development of recurrent or new AK. Field cancerization theory postulates that a large area of skin surrounding AK is also at increased risk for possible malignant transformation because it has been exposed to the same ultraviolet light for a long time. Thus, those therapies which work in a larger field have the potential to address subclinical damage, reducing AK recurrence rates and potentially reducing the risk of squamous cell carcinoma development.

There are various treatment regimens available in AK

1. Conventional – Imiquimod 5% cream to be applied thrice/week (every alternate day) for about 8–16 weeks.[4]
2. Modified regimen – Imiquimod 5% cream to be applied thrice/week every alternate day for 4 weeks which is followed by rest for 4 weeks. This whole process constitutes 1 cycle. Up to three cycles have shown better results with complete remission and lesser cutaneous side effects than the conventional regimen.[17]
3. Combination with cryotherapy – One session of cryotherapy consists of two sprays of liquid nitrogen for 5 second each with a rest period of 5 s in between sprays. This is followed by 3.75% imiquimod cream daily for 2 weeks which is followed by 2 weeks drug-free period after which cream is again applied daily for 2 weeks.[18]

The comparison of different modalities for AK is shown in Table 3.

Superficial BCC

BCC is a common cutaneous neoplasm that very rarely metastasises, but if neglected, it can have a locally aggressive course with destruction of underlying tissues. Although Mohs micrographic surgery remains the gold standard for the treatment of BCC, imiquimod can also be used in selected cases. For BCC, an additional mechanism of imiquimod has been suggested which occurs by blocking the activation of

Table 2: Comparison of various topical treatment modalities for anogenital warts.

Topical medication	Imiquimod cream	Podophyllotoxin	Podophyllin	Cryotherapy	Tri chloroacetic acid
Duration of use	4-16 weeks	Upto 4 weeks	Upto 6 weeks	Upto 7 weeks	Upto 7 weeks
Mode of administration	Self administered	Self administered	Applied by a healthcare professional	Applied by a healthcare professional	Applied by a healthcare professional
Course of therapy	3 times a week before bedtime, duration depends on response and wart clearance.	Apply twice daily for 3 consecutive days, followed by 4 days of no therapy	Apply every 1 to 2 weeks with vaseline in the periphery and left on for 4–6 h before washing off	Freezing of each wart is done separately and repeated every week	Multiple applications are done over a week interval
Clearance rate	Approx 56%[7]	45 to 77%[8]	30-80%[12]	79-88%	70-80%[10]
Recurrence rate	13%[7]	38%[9]	Variable	25-40%[15]	36%[11]
Side effects	Local skin reactions (redness, itching, burning) - Flu-like symptoms (rarely)	Skin irritation, redness, or burning - Mild flu-like symptoms (rarely)	Skin irritation, ulceration, or burning - Potential systemic toxicity (rarely)[13,14]	Pain or discomfort during the procedure - Blistering or ulceration of the treated area (temporary)	Skin irritation, redness, or burning - Potential for scarring

Table 3: Comparison of various topical treatment modalities for actinic keratoses.

Topical medication	Dosage form	Treatment duration	Application frequency	Common side effects	Clearance rates	Recurrence rates
5- Fluorouracil	Cream	2 to 4 weeks	Once or twice daily, as directed	Local skin reactions (redness, peeling)	67-96%	54%
Imiquimod	Cream	6 to 16 weeks	3 times a week	Local skin reactions (redness, itching)	Approx. 68%	10.5%
Ingenol mebutate	Gel	2 or 3 consecutive days	Single course application	Local skin reactions (redness, swelling)	Approx. 48%	-
Diclofenac	Gel	60 to 90 days	Twice daily, as directed	Local skin reactions (redness, itching)	Approx. 75%	-

Table 4: Comparison of various topical treatment modalities for superficial basal cell carcinoma (BCC).

Topical treatment	Dosage form	Treatment duration	Application frequency	Common side effects	Clearance rates	Recurrence rates
Imiquimod 5%	Cream	6 to 12 weeks	5 times a week	Local skin reactions (redness, itching)	Approx. 86%	2%
5-Fluorouracil	Cream	2 to 6 weeks	Twice daily	Local skin reactions (redness, peeling)	Approx. 93%	18%
Diclofenac	Gel	6 to 12 weeks	Twice daily, as directed	Local skin reactions (redness, itching)	64%	-
Photodynamic therapy	Solution	1 to 2 sessions	Single application or with light therapy	Local skin reactions (burning, stinging)	87%	14%

the Hedgehog/glioma-associated oncogene (GLI) signalling pathway (important in the pathogenesis of BCC).[19]

Dosing – 5% imiquimod cream applied 5 times a week for 6 weeks (~75% clearance) in immunocompetent adults have been approved by FDA for superficial BCC with maximum tumour diameter <2 cm in 2004.[20] Thicker lesions have a low response rate. Imiquimod provides a good alternative for the people who are unwilling or unfit for surgery, although the success rate is lower than Mohs micrographic surgery (99%). When compared to photodynamic therapy, imiquimod may be more effective in treating superficial BCC [Table 4]. Imiquimod has shown excellent results in patients with multiple BCC and in xeroderma pigmentosum patients with only minor side-effects.

OFF LABEL DERMATOLOGICAL USES

Common warts

Imiquimod monotherapy has proved to be less efficient for treating cutaneous warts due to its decreased penetrance and absorption through wart tissue. Hence, combining it with other modalities of cytodestructive treatments such as cryotherapy, salicylic acid and occlusion can increase its penetrance thus increasing its efficiency and hence, better outcome of common warts. It may also serve as a good alternative in the management of recalcitrant warts in immunosuppressed patients.

Molluscum contagiosum

Molluscum is generally regarded as a self-limiting disease; however, its treatment is generally advised as it has a potentially protracted course and due to the risk of superinfection, scarring, autoinoculation and transmission to other members of the community. Topical imiquimod once daily under occlusion has shown remission within 3–8 weeks of treatment with only mild-to-moderate irritation in the application area.[21]

Keloids

Imiquimod causes an indirect increase in the production of interferon alpha and, possibly, transforming growth factor beta-3 at the site of application which decreases collagen and extracellular matrix component deposits involved in scar formation. It acts as a useful adjunct to surgical resection by decreasing recurrence. It is applied once daily for around 8 weeks at the site of surgical excision of the keloid has shown minimal recurrences following excision.[22]

Nodular and morphoeic basal cell carcinoma

Imiquimod, 5% cream can be used as an alternative in patients with small nodular and morphoeic BCCs who are poor candidates for surgery. According to a study, topical 5% imiquimod cream is well tolerated and most effective in treating nodular BCC when applied once daily for 6–12 weeks.[23]

Cutaneous malignancies other than BCC

Imiquimod has been found to be useful in many cutaneous malignancies and can be used as a standalone or as an adjunct to on-going treatment [Table 5].[24-26]

Mycosis fungoides

Imiquimod has proved to be an effective therapy for early-stage disease of cutaneous T-cell lymphomas, whether used alone or in combination with systemic immunomodulatory therapy. This is well tolerated and associated with a histologic and clinical response rate of 50% in patch and plaque stage.[27]

Table 5: Imiquimod in various cutaneous malignancies.

Type of lesion	Treatment protocol	Treatment duration	Response
Bowen disease of skin	Imiquimod 5% cream once daily application	upto 16 weeks	Most patients had resolved and reported no residual SCC in situ in the post treatment biopsy specimen 6 weeks after stopping treatment
Vulvar intraepithelial neoplasia	Imiquimod was applied to lesion *3-5 days/wk along with application over 1cm of normal skin	upto 16 weeks	Most of the patients showed complete response while some had moderate response. Though surgery is currently the standard of care for the treatment of VIN but for those patients who want to preserve sexual function, conservative treatment like imiquimod is beneficial.[24]
Erythroplasia of Queyrat (EQ)	Imiquimod 5% to be applied 3-7 times/week	upto 24 weeks	Good clinical response noted
Anal intraepithelial neoplasia	Imiquimod 5% to be applied 3 times per week	16 weeks	Good initial response rates and there was improvement in HPV type and DNA load. Combination of topical and invasive procedures could offer the best benefit for treatment of AIN.[25]
Invasive SCC	Imiquimod 3 times a week	12 weeks	Good response with no evidence of residual tumour at 6 months follow up.
Metastatic melanoma	3 times weekly imiquimod as an adjunct with continuing treatment. 3 times a week application as a stand alone treatment	12 weeks 16 weeks	Imiquimod caused complete clearing in imiquimod-treated cutaneous metastatic lesions. Complete clearance of the lesions with recurrence at 15 months follow up.[26]

VIN: Verrucous intraepithelial neoplasia, HPV: Human papilloma virus, AIN: Anal intraepithelial neoplasia, SCC: Squamous cell carcinoma

Infantile haemangioma (IH)

It has been reported to be efficacious in the treatment of IH due to its ability to induce the production of tissue inhibitor of matrix metalloproteinase which has antiangiogenesis property. There has been significant improvement in superficial IH and little improvement in mixed IH with no or very less changes in deep hemangiomas.[28]

CONTRAINDICATIONS

There are no known absolute contraindications to the use of imiquimod.

Relative contraindications include:

- Patients with known benzyl alcohol hypersensitivity or paraben hypersensitivity
- Pregnant and lactating females
- Patients with pre-existing autoimmune diseases
- Photosensitivity
- Graft versus host disease.

ADVERSE EFFECTS

There have been no serious side effects of imiquimod application. Most frequently reported side effects include transient erythema, pruritus and burning sensation over the site of application. Dizziness, fatigue and angioedema have been reported by very few people [Table 6].

PRECAUTIONS

- Treated area should not be covered with tight bandage or dressing
- Sexual (oral, anal and genital) contact should be avoided while the cream is on the skin as imiquimod cream may weaken condoms and vaginal diaphragms
- Uncircumcised men should pull the foreskin back and clean it daily and before each treatment
- It should not be applied in or near the eyes, lips, nostrils, vagina or anus
- Patients should be asked to dispose of any open packets
- In case of severe local skin reaction to cream, the cream should be removed and area is to be washed with mild soap and water and resumed after the skin reaction has subsided.

Table 6: Adverse effects of imiquimod

Most frequent	Less frequent	Rare
Erythema	Diarrhoea	Dizziness
Pruritus	Headache	Fatigue
Burning sensation	Myalgia	Fever
Scaling and dryness	Upper respiratory tract infection	Lymphadenopathy
Flu like symptoms	Severe erythema	Angioedema

CONCLUSION

Imiquimod being topical, is easy to use, self administered thus decreases the number of hospital visits and increases the compliance. It has good tolerability profile with the option of breaks from treatment as required for local skin reactions which makes it a good non invasive alternative as compared to the other destructive modalities available all together. Also in patients, who have failed to respond to other therapeutic modalities or who have had recurrence following standard therapy, or who are medically unfit for surgery, imiquimod may be beneficial with a close follow up routine.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Eedy DJ. Imiquimod: A Potential Role in Dermatology? Br J Dermatol 2002;147:1-6.
2. Leverkus M. Imiquimod: Unexpected Killer. J Invest Dermatol 2004;122:15-6.
3. Beutner KR, Geisse JK, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic Response of Basal Cell Carcinoma to the Immune Response Modifier Imiquimod 5% Cream. J Am Acad Dermatol 1999;41:1002-7.
4. Navi D, Huntley A. Imiquimod 5 Percent Cream and the Treatment of Cutaneous Malignancy. Dermatol Online J 2004;10:4.
5. Diamantis ML, Bartlett BL, Tyring SK. Safety, Efficacy, and Recurrence Rates of Imiquimod Cream 5% for Treatment of

Anogenital Warts. Skin Ther Lett 2009;14:1-3, 5.
6. Stone KM. Human Papillomavirus Infection and Genital Warts: Update on Epidemiology and Treatment. Clin Infect Dis 1995;20(suppl 1):S91-7.
7. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, *et al*. Self-Administered Topical 5% Imiquimod Cream for External Anogenital Warts. HPV Study Group. Human Papillomavirus. Arch Dermatol 1998;134:25-30.
8. Lacey CJ, Goodall RL, Tennvall GR, Maw R, Kinghorn GR, Fisk PG, *et al*. Randomised Controlled Trial and Economic Evaluation of Podophyllotoxin Solution, Podophyllotoxin Cream, and Podophyllin in the Treatment of Genital Warts. Sex Transm Infect 2003;79:270-5.
9. Edwards A, Atma-Ram A, Thin RN. Podophyllotoxin 0.5% v Podophyllin 20% to Treat Penile Warts. Genitourin Med 1988;64:263-5.
10. Abdullah AN, Walzman M, Wade A. Treatment of External Genital Warts Comparing Cryotherapy (Liquid Nitrogen) and Trichloroacetic Acid. Sex Transm Dis 1993;20:344-5.
11. Godley MJ, Bradbeer CS, Gellan M, Thin RN. Cryotherapy Compared with Trichloroacetic Acid in Treating Genital Warts. Genitourin Med 1987;63:390-2.
12. Wiley DJ. Genital Warts. Clin Evid 2003;9:1741-53.
13. Petersen CS, Weismann K. Quercetin and Kaempherol: An Argument against the Use of Podophyllin? Genitourin Med 1995;71:92-3.
14. Scheinfeld N, Lehman DS. An Evidence-based Review of Medical and Surgical Treatments of Genital Warts. Dermatol Online J 2006;12:5.
15. Yanofsky VR, Patel RV, Goldenberg G. Genital Warts: A Comprehensive Review. J Clin Aesthet Dermatol 2012;5:25-36.
16. Gupta AK, Cooper EA, Abramovits W. Zyclara (Imiquimod) Cream, 3.75%. Skinmed 2010;8:227-9.
17. Salasche SJ, Levine N, Morrison L. Cycle Therapy of Actinic Keratoses of the Face and Scalp with 5% Topical Imiquimod Cream: An Open-label Trial. J Am Acad Dermatol 2002;47:571-7.
18. Goldenberg G, Linkner RV, Singer G, Frankel A. An Investigator-Initiated Study to Assess the Safety and Efficacy of Imiquimod 3.75% Cream When Used after Cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms. J Clin Aesthet Dermatol 2013;6:36-43.
19. Wolff F, Loipetzberger A, Gruber W, Esterbauer H, Aberger F, Frischauf AM. Imiquimod Directly Inhibits Hedgehog Signalling by Stimulating Adenosine Receptor/Protein Kinase A-Mediated GLI Phosphorylation. Oncogene 2013;32:5574-81.
20. Jobanputra KS, Rajpal AV, Nagpur NG. Imiquimod. Indian J Dermatol Venereol Leprol 2006;72:466-9.
21. Badavanis G, Pasmatzi E, Monastirli A, Georgiou S, Tsambaos D. Topical Imiquimod is an Effective and Safe Drug for Molluscum Contagiosum in Children. Acta Dermatovenerol Croat 2017;25:164-6.
22. Khandpur S, Sharma VK, Sumanth K. Topical Immunomodulators in Dermatology. J Postgrad Med 2004;50:131-9.
23. Shumack S, Robinson J, Kossard S, Golitz L, Greenway H, Schroeter A, *et al*. Efficacy of Topical 5% Imiquimod Cream for the Treatment of Nodular Basal Cell Carcinoma Comparison of Dosing Regimens. Arch Dermatol 2002;138:1165-71.
24. Frega A, Sesti F, Sopracordevole F, Biamonti A, Scirpa P, Milazzo GN, *et al*. Imiquimod 5% Cream Versus Cold Knife Excision for Treatment of VIN 2/3: A Five-year Follow-up. Eur Rev Med Pharmacol Sci 2013;17:936-40.
25. Fox PA, Nathan M, Francis N, Singh N, Weir J, Dixon G, *et al*. A Double-blind, Randomized Controlled Trial of the Use of Imiquimod Cream for the Treatment of Anal Canal High-grade Anal Intraepithelial Neoplasia in HIV-Positive MSM on HAART, with Long-term Follow-up Data Including the Use of Open-label Imiquimod. AIDS 2010;24:2331-5.
26. Wolf IH, Smolle J, Binder B, Cerroni L, Richtig E, Kerl H. Topical Imiquimod in the Treatment of Metastatic Melanoma to Skin. Arch Dermatol 2003;139:273-6.
27. Deeths MJ, Chapman JT, Dellavalle RP, Zeng C, Aeling JL. Treatment of Patch and Plaque Stage Mycosis Fungoides with Imiquimod 5% Cream. J Am Acad Dermatol 2005;52:275-80.
28. Ho NT, Lansang P, Pope E. Topical Imiquimod in the Treatment of Infantile Hemangiomas: A Retrospective Study. J Am Acad Dermatol 2007;56:63-8.

How to cite this article: Gupta S, Agarwal P, Baxi K, Nyati A. Imiquimod: Newer Perspectives to an Old Drug. Indian J Postgrad Dermatol. 2024;2:10-6. doi: 10.25259/IJPGD_99_2023